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The Total Synthesis of Pamamycin 607. 1. Synthesis of a C1'-C11' Synthon.

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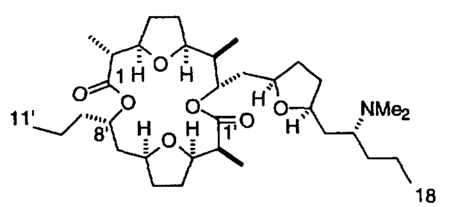
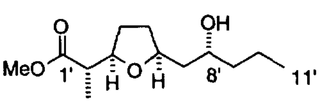
Abstract: The synthesis of a C1'-C11' synthon **2** of pamamycin-607 starting from alcohol **3** in ten steps is reported. Copyright © 1996 Elsevier Science Ltd

The pamamycins form a group of homologous, naturally-occurring macrodiolides.[1] They possess a remarkable range of chemical and biological activity, including antibiotic properties and anionophoric behaviour.[2-5] In our planned synthesis of the homologue of molecular weight 607 (**1**), we have identified the C8'-epimer of the C1'-C11' subunit as a useful intermediate (synthon **2**). Our intention is to couple this with the C1-C18 subunit using a process which would involve inversion at C8'.[6] Should this process prove difficult, inversion[7] of C8' prior to macrolactonisation[8] of the subunits could be employed.

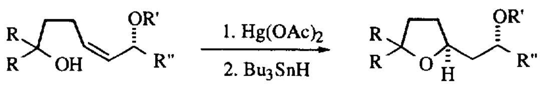


1 Pamamycin 607



2 C1'-C11' synthon

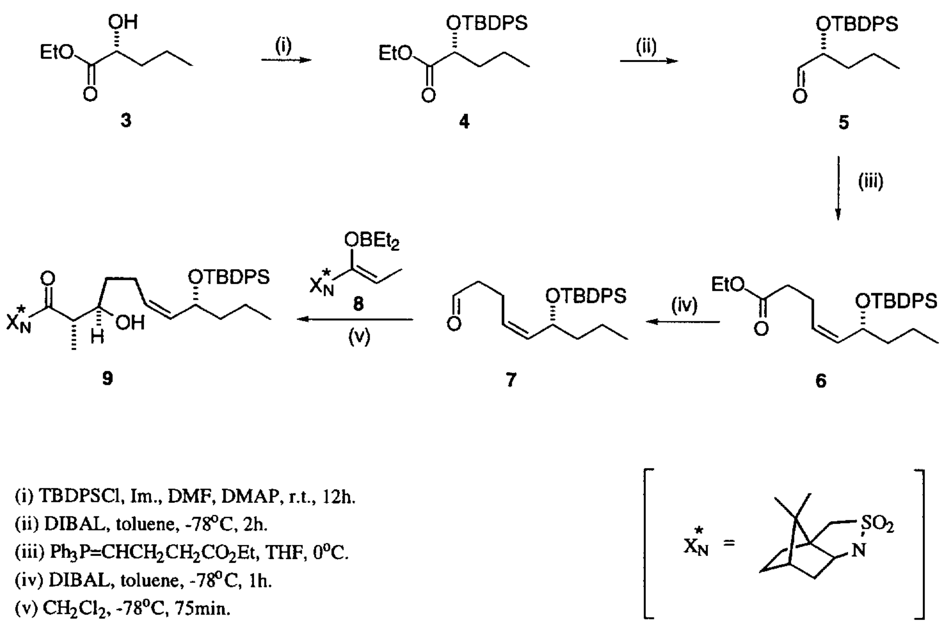
We have recently carried out studies[9,10] on the diastereoselectivity associated with the ring closure of γ-hydroxyalkenes bearing a remote, secondary allylic ether to give substituted tetrahydrofurans (Scheme 1). We found good to excellent diastereoselectivity ranging from 6:1 up to 20:1. Herein we report an extension of this methodology to the synthesis of the C1'-C11' synthon (**2**).



Scheme 1

General scheme for intramolecular oxymercuration/demercurations.

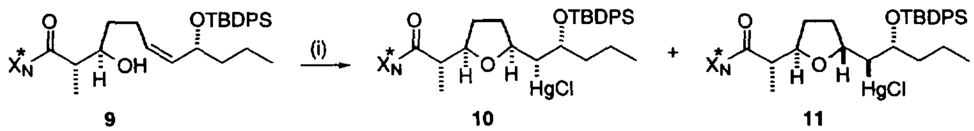
The synthesis of the ring closure precursor **9** was accomplished in five steps from the known ethyl (2*S*)-2-hydroxypentanoate **3** (ee. 85-89%)[11,12] as outlined in Scheme 2. Protection of the secondary alcohol as its *tert*-butyldiphenylsilyl (TBDPS) ether (96%), followed by diisobutylaluminium hydride (DIBAL) reduction (95%) gave the aldehyde **5**. *Z*-Selective olefination (51%) provided alkene **6** with good selectivity (*Z*:*E* =89:11). A second DIBAL reduction proceeded cleanly to give the new aldehyde **7** in 97% yield. This alkenal was then subjected to a *syn*-selective aldol reaction using the diethylboron enolate **8**[13] of Oppolzer's camphor-derived N-propionylsultam to give the required major (*syn*) product **9** (54%).[14]



(i) TBDPSCl, Im., DMF, DMAP, r.t., 12h.
(ii) DIBAL, toluene, -78°C, 2h.
(iii) $Ph_3P{=}CHCH_2CH_2CO_2Et$, THF, 0°C.
(iv) DIBAL, toluene, -78°C, 1h.
(v) CH_2Cl_2, -78°C, 75min.

Scheme 2 Synthesis of ring closure precursor **9.**

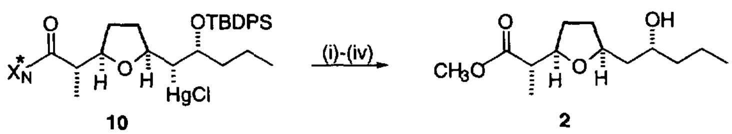
Ring closure was then effected using the intramolecular oxymercuration procedure outlined earlier.[9,10] Thus, when an acetonitrile solution of alkenol **9** was treated with 1.5 equivalents of mercury(II)acetate for 18h at room temperature the products, isolated as their chloromercurial derivatives, were obtained in a 6:1 ratio in favour of the desired diastereomer **10** (Scheme 3). This molecule, which could be easily separated from **11** by chromatography on silica gel, contains the complete skeleton of the target synthon (**2**) with all the stereocentres correctly installed.



(i) (a) $Hg(OAc)_2$, CH_3CN, r.t., 18h; (b) Aq. NaCl.

Scheme 3 Intramolecular oxymercuration of alkenol **9**.

Four straightforward functional group manipulations remained to complete the synthesis of **2**. Reductive demercuration with tributylstannane and AIBN[15] proceeded in a 93% yield. Removal of the chiral auxiliary was achieved by hydrolysis with alkaline hydrogen peroxide[13] and the crude reaction mixture was directly esterified with an excess of diazomethane in 46% yield over 2 steps. Finally, desilylation with tetrabutylammonium fluoride produced the target molecule **2** in 56% yield [$[a]_D^{20}$ -6.0° (*c* 0.5, $CHCl_3$)][16] (Scheme 4).



(i) Bu_3SnH, AIBN, toluene; (ii) 30% Aq. H_2O_2, LiOH, THF; (iii) CH_2N_2, Et_2O; (iv) TBAF, THF, r.t.

Scheme 4 Completion of the synthesis of **2**.

The application of this approach to the synthesis of the larger subunit[17] of pamamycin 607 is under way in our laboratories.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. McCann, P. A.; Pogell, B. M. *J. Antibiot.* **1979**, *32*, 673-678.
2. Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot.* **1988**, *41*, 1196-1204.
3. Stengel, C.; Reinhardt, G.; Grafe, U. *J. Basic Microbiol.* **1992**, *32*, 339-345.
4. Walkup, R. D.; Kim, S. W. *J. Org. Chem.* **1994**, *59*, 3433-3441.
5. Chou, W.; Pogell, M. *Biochem. Biophys. Comm.* **1981**, *100*, 344-350.
6. Bartlett, P. A.; Meadows, J. D. *J. Am. Chem. Soc.* **1984**, *106*, 5304-5311.
7. Warm, A.; Vogel, P. *Helv. Chimica Acta.* **1987**, *70*, 690-699.
8. Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 2287-2288.
9. Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, G. *Tetrahedron Lett.* **1995**, *36*, 463-466.
10. Bratt, K.; Garavelas, A.; Hockless, D. C. R.; Perlmutter, P.; Westman, G. *J. Org. Chem.* **1996**, *61*, in press.
11. Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Org. Chem.* **1984**, *106*, 1531-1533.
12. Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384-1394.
13. Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. J. *J. Am. Chem. Soc.* **1990**, *112*, 2767-2772.
14. Minor impurities (due to the incomplete enantioselectivity in the reduction leading to hydroxyester **3**) were difficult to separate and were carried through to compound **2** where they could be completely removed.
15. Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.
16. Data for **2**: $[a]_D^{20}$ -6.0° (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.0 Hz, 3H, CH_3), 1.22 (d, *J*=7.0 Hz, CH_3), 1.31-1.39 (m, 2H, CH_2), 1.41-1.51 (m, 4H, CH_2x2), 1.60-1.74 (m, 2H, CH_2), 1.91-2.07 (m, 2H, CH_2), 2.57 (p, *J*=7.1 Hz, 1H, $CHCH_3$,) 3.54 (bs, 1H, OH), 3.69 (s, 3H, OCH_3), 3.70-3.83 (m, 1H, CHOTBDPS), 3.99-4.06 (m, 2H, CHOx2). ^{13}C NMR (50 MHz) δ 174.8 (C=O); 80.9 (CHO), 80.4 (CHO), 71.5 (CHOH), 51.7 (OCH_3); 44.8 ($CHCH_3$); 42.7 (CH_2CO); 39.7 (CH_2CO); 31.9 (CH_2COH); 28.6 (CH_2); 18.7 (CH_2); 14.1 (CH_3CH); 13.9 (CH_3). MS (CI): 245 (M+1, 32%), 228(20), 227(100), 209(20), 195(40), 157(80), 139(28), 71(15), 57(20). HRMS (CI) Calcd. for $C_{13}H_{24}O_4$: 245.176. Found 245.176 ± 0.002.
17. For an alternative approach to an intermediate for this subunit, see: Walkup, R. D.; Kim, Y. S. *Tetrahedron Lett.* **1995**, *36*, 3091-3094.

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